REPLY

The letter from Dr. Aguiar-Souto and colleagues has been reviewed and their comments are very much appreciated. The American College of Cardiology/American Heart Association (ACC/AHA) 2005 guidelines for chronic heart failure ascribed a class IIa, level of evidence A, recommendation to the adjunctive use of isosorbide dinitrate/hydralazine to standard therapy in patients with persistent symptoms of heart failure without a race designation. The section of the guidelines addressing special populations likewise ascribed a class IIa, level of evidence A, recommendation to the use of combined vasodilator therapy in addition to standard therapy in blacks with functional class III or IV heart failure (1).

The rationale for this classification is based on the preponderance of data demonstrating the benefit of combined vasodilator therapy in symptomatic heart failure. The Vasodilator Heart Failure Trials (V-HeFT I and V-HeFT II) demonstrated a mild survival advantage for this regimen in V-HeFT I and improvement in the important surrogate end points of exercise capacity and left ventricular function in V-HeFT II. A subsequent retrospective analysis of both trials demonstrated that the majority of the benefit was seen in black patients, but the effect was not absent in the non-black cohort (2). The significant results now demonstrated in the African American Heart Failure Trial (A-HeFT) confirm the advantage of this regimen (3). A strongly held opinion of the guideline writing committee is that there are insufficient data to assert that race alone is the operative variable that determines responsiveness to this regimen. Thus, two clinical trials, V-HeFT I and A-HeFT, demonstrate benefit in patients with symptomatic heart failure, and a third trial, V-HeFT II, is consistent with a favorable effect of vasodilator therapy in symptomatic heart failure.

A class IIa recommendation states that a given treatment or intervention "is reasonable" and that the risk-benefit ratio is decidedly favorable. Level A evidence for a class IIa recommendation requires multiple positive data sources, but also allows for a recommendation in favor of therapy despite incongruent data from smaller datasets and retrospective analyses. Given multiple trials demonstrating the benefit of combined vasodilator therapy in diverse populations, the class recommendation appears reasonable for both the general population and for blacks with symptomatic heart failure, and the level of evidence is indeed consistent with the several confirmatory trials.

The class IIb recommendation for the addition of an angiotensin receptor antagonist to already effective therapy is reasonable based primarily on a morbidity-only advantage seen in the CHARM-Added trial (4). The data regarding the use of nebivolol had not been published during the deliberations of the guideline writing committee; thus, they were not available to be incorporated into the 2005 statement.

***Clyde W. Yancy, MD, FACC, FAHA, FACP**

*UT Southwestern Medical Center
5323 Harry Hines Boulevard
Dallas, Texas 75390-9047
E-mail: clyde.yancy@utsouthwestern.edu

doi:10.1016/j.jacc.2006.04.019

REFERENCES

1. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult. Available at: http://www.acc.org/clinical/guidelines/failure/index.pdf. Accessed February 2006.
2. Carson P, Ziesche S, Johnson G, Cohn JN, for the Vasodilator-Heart Failure Trial Study Group. Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. J Card Fail 1999;5:178–87.
3. Taylor AL, Ziesche S, Yancy C, et al. for the African-American Heart Failure Trial investigators. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004;351:2049–57.
4. McMurray JJ, Östergren J, Swedberg K, et al. for the CHARM investigators and committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003;362:767–71.

China's Role in International Cardiology

Dr. DeMaria's excellent editorial on international cardiology (1) touches on several aspects that deserve further comments and amplification from China's point of view. After all, one of every five persons on this planet lives in China (2).

First, the *Journal of the American College of Cardiology* (*JACC*) is an excellent example of international cardiology (1). It may be of interest to Dr. DeMaria to know that *JACC* is the second most frequently cited foreign cardiologic journal referenced in articles published in the *Chinese Journal of Cardiology,* the official cardiology journal in China (2).

Second, Dr. DeMaria commented on the spectrum of cardiovascular diseases among different countries worldwide. While there are indeed such differences as illustrated by the examples cited by Dr. DeMaria, the gaps are getting narrower. For example, the metabolic syndrome has reached near epidemic proportions in the U.S., as Dr. DeMaria (1) mentioned. It has also become a problem in China where the prevalence of metabolic syndrome is 13.3% (12.7% in male and 14.2% in female subjects) (3,4). In China, obesity—which has become the nation's newest health risk (5)—is the principal reason for the increased prevalence of the metabolic syndrome (3,4). It is a paradox to note that, whereas being underweight is one of the major causes of death in rural China (6), being overweight is one of the major concerns in urban China (2).

Third, China is the most populous country in the world, with over 1.3 billion people. Because of this enormous population and a very low migration rate, it is an ideal country to conduct clinical trials. As a matter of fact, the second largest trial of treatment of acute myocardial infarction (AMI) in the world and the largest clinical trial ever underaken in China, COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial), has just been published (7). The results of this mammoth study, involving 45,852 patients in China, will undoubtedly influence the treatment of AMI throughout the world in the future.

Finally, I wish to echo what Dr. DeMaria said, namely that the world is getting smaller. As my mentor, the late Dr. Paul D. White, said, cardiology knows no international boundary and is the world's best goodwill ambassador (8).

Tsung O. Cheng, MD, FACC

*The George Washington University
Medical Center
Department of Medicine
2150 Pennsylvania Avenue, NW
Washington, DC 20037
E-mail: tcheng@mfa.gwu.edu

doi:10.1016/j.jacc.2006.04.020

REFERENCES

1. DeMaria AN. Editors page: international cardiology. J Am Coll Cardiol 2005;46:1580–1.
2. Cheng TO. The current state of cardiology in China. Int J Cardiol 2004;96:425–39.
3. Cheng TO. Metabolic syndrome in China. Circulation 2004;109:e180.
4. Cheng TO. The metabolic syndrome, formerly called metabolic 'syndrome X.' Am J Cardiol 2004;94:148–9.
5. Cheng TO. Obesity is the newest health risk in modern China. Lancet 2005. Available at: http://www.thelancet.com/journals/lancet/article/PIIS0140673605673448/comments?actio. Accessed October 7, 2005.
6. He J, Gu D, Wu X, et al. Major causes of death among men and women in China. N Engl J Med 2005;353:1124–34.
7. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. Lancet 2005;366:1607–21.
8. Cheng TO, Paul D. White Lecture: Cardiology in People's Republic of China. In Russek HI, editor. New Horizons in Cardiovascular Practice. Baltimore, MD: University Park Press, 1975:1–27.

Renal Artery Stenting Following Unsuccessful Balloon Angioplasty

As an interventional cardiologist I read with great interest the Rocha-Singh et al. (1) paper regarding renal artery stenosis and revascularization. I think an excellent job was done in delineating the usual indications. However, new ideas have recently surfaced regarding how to determine the significance of a lesion, and more information is now available regarding the physiology of a significant renal artery stenosis.

The radiologist and vascular surgeon, in general, are often not conversant with the adverse effects of a hyperrenin state, congestive heart failure, unstable angina, and progression of atherosclerosis. Unfortunately, many well-known experts, in the face of a hemodynamically significant lesion, have over the years, advocated delaying stenting until creatinine is elevated. However, when creatinine is ≥2 mg/dl, (12.5% of study patients) mortality has been shown to be grossly increased in studies where patients are followed over a four-year period (2,3). Half of renal function may be lost before creatinine is elevated, and there should be an obvious attempt to find these patients before renal function has deteriorated and mortality and morbidity have escalated (4). Renal artery Doppler, renal scan, and creatinine clearance will give subtle clues to early loss of kidney function, and beta-natriuretic peptide may be elevated.

The "unobvious" patients needing revascularization may be the patients with elevated creatinine without hypertension, often in the face of peripheral vascular disease and coronary disease; unilateral kidney shrinkage without significant hypertension; or sudden significant increase in blood pressure. The number of medications should be removed as a parameter for interventions if the patient is treated with clonidine, labetalol, or minoxidil, as moderate doses of these drugs may be equivalent to multiple medications.

Moreover, it needs to be emphasized that the significance of the lesion is often much greater than its angiographic appearance and can be confirmed by flow-wire measurement of pressure gradients and fractional flow reserve (FFR) (5), with these measurements perhaps supplanting 4F catheter gradient measurements. (French size of catheter used for gradient measurement is not discussed in the study.) Then there is the asymptomatic patient with normal creatinine, with a high-grade renal artery stenosis and an extremely high gradient. Obviously the patient with a hyperrenin state will undergo significant progression of diffuse atherosclerosis and progression of arteriolar nephrosclerosis in the contralateral kidney (6). This patient should be revascularized.

These comments should be read in context, as the ASPIRE-2 study was performed 8 to 10 years ago. It is hoped that new studies regarding further research into FFR with varying degrees of renal stenosis, cytokine release in the presence of renal artery stenosis, and the effects of progression of diffuse atherosclerosis, congestive heart failure, and unstable angina will be delineated.

Wood M. Deming, MD, FACC, FSCAI

*Regional Cardiology Consultants
111 Stonebridge Boulevard
Jackson, Tennessee 38305
E-mail: wooddeming@regionalcardiology.com

doi:10.1016/j.jacc.2006.04.025

REFERENCES

1. Rocha-Singh K, Jaff MR, Rosenfield K, and the ASPIRE-2 Trial Investigators. Evaluation of the safety and effectiveness of renal artery stenting after unsuccessful balloon angioplasty: the ASPIRE-2 study. J Am Coll Cardiol 2005;46:776–83.
2. Conlon P, Athirakul K, Kovalik E, et al. Survival in renal vascular disease. J Am Soc Nephrol 1998;9:252–6.
3. Watson P, Hadjipetrou P, Cox S, et al. Effect of renal artery stenting on renal function and size in patients with atherosclerotic renovascular disease. Circulation 2000;102:1671–7.
4. Sos T, Trost D. The importance of renal artery stenting in ischemic nephropathy. Endovascular Today 2003;Nov/Dec:44.
5. Subramanian R, White C, Rosenfield K, et al. Renal fractional flow reserve: a hemodynamic evaluation of moderate renal artery stenoses. Catheter Cardiovasc Interv 2005;64:480–6.
6. Dean R, Kieffer R, Smith B, et al. Renovascular hypertension. Arch Surg 1981;116:1408–15.